



Patent
Attorney's Docket No. 016800-448

1651
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
)
Dominique BERNARD et al.) Group Art Unit: 1651
)
Application No.: 09/884,953) Examiner: Jon P. Weber
)
Filed: June 21, 2001) Confirmation No.: 3212
)
For: ISOLATED CATHEPSIN L TYPE)
CYSTEINE PROTEASES AND)
REDUCING INTERCORNEOCYTE)
COHESION/PROMOTING)
DESQUAMATION THEREWITH)

AMENDMENT/REPLY TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed is a Supplemental Response for the above-identified patent application.

- ☐ A Petition for Extension of Time is also enclosed.
- ☐ A Terminal Disclaimer and the ☐ \$55.00 (2814) ☐ \$110.00 (1814) fee due under 37 C.F.R. § 1.20(d) are also enclosed.
- ☒ Also enclosed is/are Annexes 1-8, Information Disclosure Statement Transmittal Letter, Information Disclosure Statement, and PTO 1449 with copies of references.
- ☐ Small entity status is hereby claimed.
- ☐ Applicant(s) requests continued examination under 37 C.F.R. § 1.114 and enclose the ☐ \$375.00 (2801) ☐ \$750.00 (1801) fee due under 37 C.F.R. § 1.17(e).
- ☐ Applicant(s) requests that any previously unentered after final amendments not be entered. Continued examination is requested based on the enclosed documents identified above.
- ☐ Applicant(s) previously submitted ___, on ___, for which continued examination is requested.

- ☐ Applicant(s) requests suspension of action by the Office until at least ___, which does not exceed three months from the filing of this RCE, in accordance with 37 C.F.R. § 1.103(c). The required fee under 37 C.F.R. § 1.17(i) is enclosed.
- ☐ A Request for Entry and Consideration of Submission under 37 C.F.R. § 1.129(a) (1809/2809) is also enclosed.
- ☒ No additional claim fee is required.
- ☐ An additional claim fee is required, and is calculated as shown below:

AMENDED CLAIMS					
	NO. OF CLAIMS	HIGHEST NO. OF CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	ADD'L FEE
Total Claims		MINUS =		× \$18.00 (1202) =	
Independent Claims		MINUS =		× \$84.00 (1201) =	
If Amendment adds multiple dependent claims, add \$280.00 (1203)					
Total Claim Amendment Fee					
If small entity status is claimed, subtract 50% of Total Claim Amendment Fee					
TOTAL ADDITIONAL CLAIM FEE DUE FOR THIS AMENDMENT					

☐ A total fee in the amount of \$ _____ is enclosed.

☐ Charge \$ _____ to Deposit Account No. 02-4800.

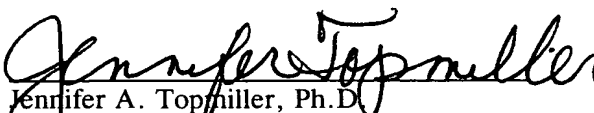
The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17, 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in duplicate.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: July 9, 2003

By:


Jennifer A. Topmiller, Ph.D.
Registration No. 50,435

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620



Patent
Attorney's Docket No. 016800-448

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In re Patent Application of)	
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Dominique BERNARD et al.)	Group Art Unit: 1651
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Application No.: 09/884,953)	Examiner: Jon P. Weber
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Filed: June 21, 2001)	Confirmation No.: 3212
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For: ISOLATED CATHEPSIN L TYPE)	
CYSTEINE PROTEASES AND)	
REDUCING INTERCORNEOCYTE)	
COHESION/PROMOTING)	
DESQUAMATION THEREWITH)	

SUPPLEMENTAL RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Amendment/Response filed June 26, 2003, submitted herewith are Annexes 1-8, inadvertently omitted from the Amendment/Response filed June 26, 2003.

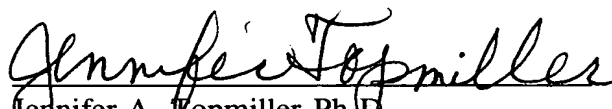
If there are any questions concerning this Supplemental Response or the application in general, the Examiner is respectfully requested to telephone Applicants' undersigned representative so that prosecution may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: July 9, 2003

By:


Jennifer A. Topmiller, Ph.D.
Registration No. 50,435

P.O. Box 1404
Alexandria, Virginia 22313-1404
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Alphabetical List of Products

[illegible]

Alphabetical List of Products

[illegible]

ANNEX 1

L'OREAL . A 97128 JP



Compute pI/Mw

Annex 2 -

CATL HUMAN (P07711)

DE CATHEPSIN L PRECURSOR (EC 3.4.22.15) (MAJOR EXCRETED PROTEIN) (MEP).
OS Homo sapiens (Human).

The computation has been carried out on the complete sequence.

Molecular weight: 37564.13

Theoretical pI: 5.32

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Complete HCL

L'OREAL

09 92128 JP



Compute pI/Mw

Annex 3

CATL HUMAN (P07711)

DE CATHEPSIN L PRECURSOR (EC 3.4.22.15) (MAJOR EXCRETED PROTEIN) (MEP).
OS Homo sapiens (Human).

The computation has been carried out on a user selected segment from position 114 to position 333 in this sequence of 333 residues.

Considered sequence fragment:

61	71	81	91	101	111	
61						APRSVDW 120
121	REKGYVTPVK	NQGQCGSCWA	FSATGALEGQ	MFRKTGRLIS	ISEQNLVDCS	GPGNEGCGNG 180
181	GLMDYAFQYV	QDNGGLDSEE	SYPYEATEES	CKYNPKYSVA	NDTGFVDIPK	QEKALMKAVA 240
241	TVGPISVAID	AGHESFLFYK	EGIFYEPDCS	SEDMDHGVLV	VGYGFEETES	DNNKYWLVKV 300
301	SWGEEWGMGG	YVKMAKDRRN	HCGIASAASY	PTV		

Molecular weight: 24169.75

Theoretical pI: 4.68

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part of HCL

L'oreal
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11 DOUTONS

Cat. No. 1911-0507

Lot No. A960711

Quantity 1 ml

Polyclonal antibody to

CATHEPSIN L

Ames



DISTRIBUTEUR

valbiotech

57, BOULEVARD DE LA VILLETTE 75010 PARIS

Tél : 33 (0)1 40 03 89 14

FAX : 33 (0)1 44 52 92 69

Host:

Sheep

Immunogén:

Highly pure Cathepsin L (EC 3.4.22.15) from human kidney

Presentation:

Liquid, Ig fraction (by selective precipitation) in PBS, pH 7.2 without preservatives

Ig concentration:

2.6 mg/ml

Assay system:

ELISA/(not tested in IHC)

Titre

To be established in end user assay system using 1/2,500 to 1/10,000 as a guide in a simple ELISA

Cross reactivity:

Minimal cross reactivity with related serum proteins. May cross react with Cathepsin L from other species.

Storage:

Aliquot and store at 4°C, avoid contamination

Associated products:

Other conjugated antibodies to other Cathepsins, Cathepsin antigens.

02/08/94/AT

For In-Vitro Research and Manufacturing Use Only



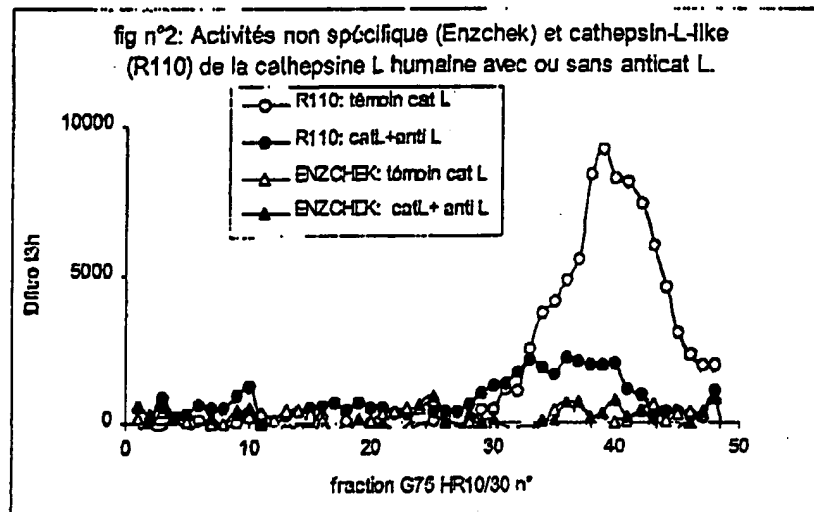
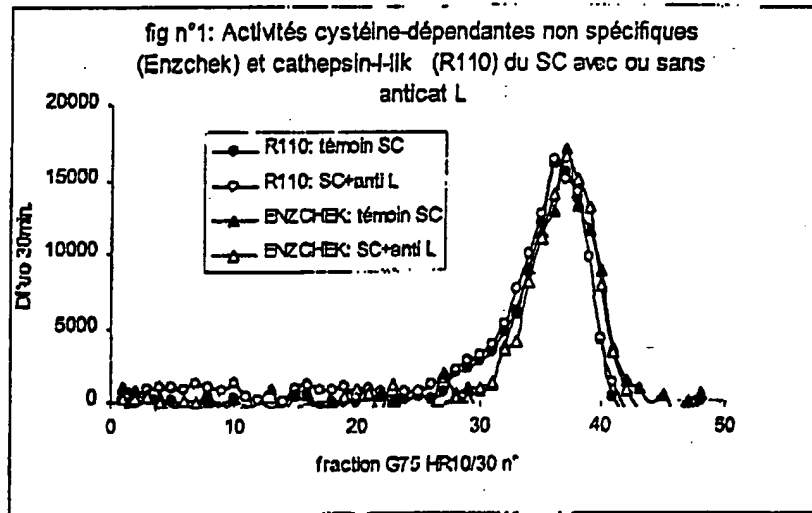
Head office: Biogenesis Ltd, 7 New Fields, Fosse BH17 0NF, England, UK Telephone: (01202) 660006 Fax: (01202) 660020
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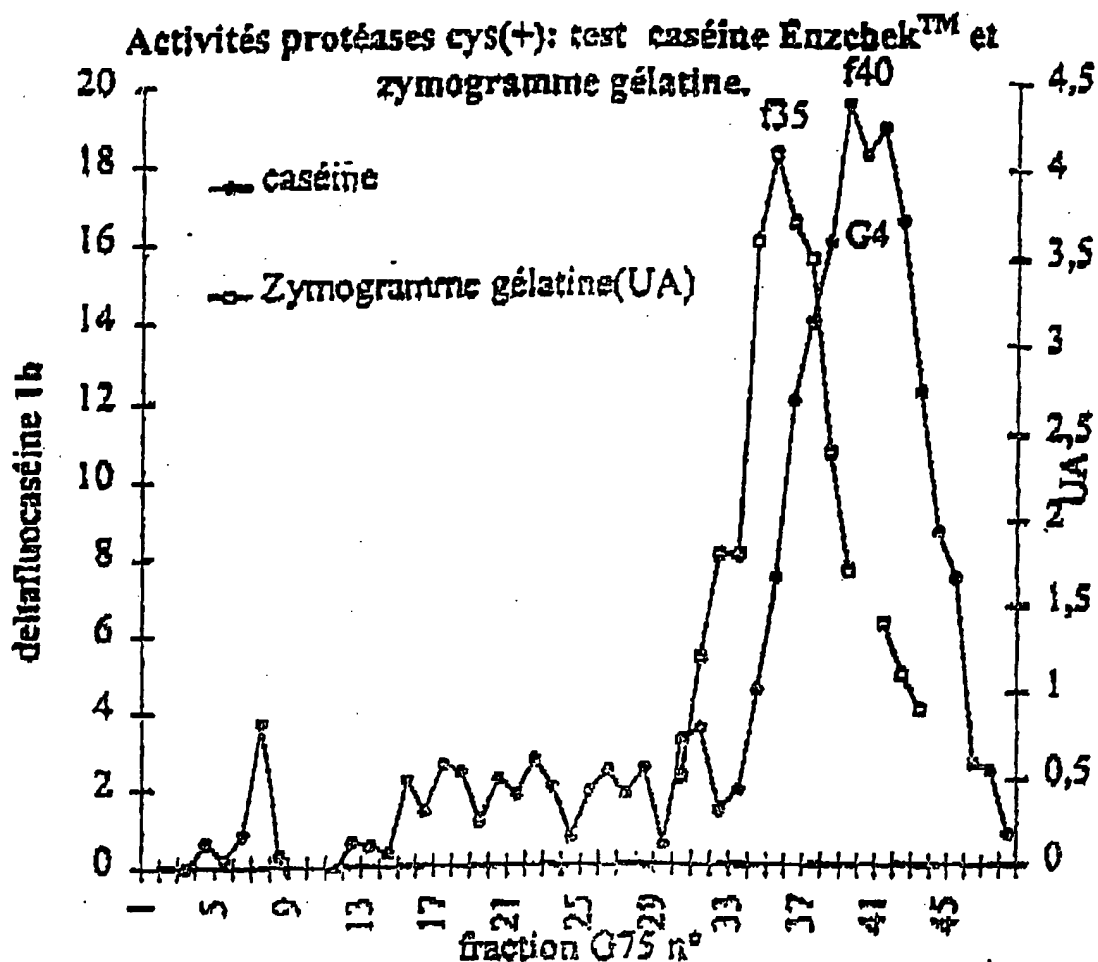
Amex 5



Conclusions :

Ces résultats prouvent que la protéase cystéine-dépendante du SC humain détectée à la fois par le test ENZCHEK et par le substrat peptidique Z(Phc-Arg)₂R110 est différente de la cathepsine L humaine car :

- 1) Elle n'est pas du tout immunoprécipitée par l'anticorps (fig n°1) alors que l'activité cathepsine L disparaît presque totalement des surnageants dans les mêmes conditions expérimentales (fig. n°2) ;
- 2) Elle a un poids moléculaire apparent plus grand que la cathepsine L comme le prouve son élution plus rapide (fig n°1/fig n°2) ;
- 3) Elle a une spécificité de substrat sans doute très différente de la cathepsine L car elle libère une fluorescence équivalente que ce soit à partir de la cystéine du test Enzchek ou à partir du peptide marqué à la Rhodamine 110 (fig. n°1) alors que l'activité cathepsine L n'est détectable dans nos conditions expérimentales que sur le substrat peptidique (fig n°2).



Amer G

G4 = our peptide .

L'OREAL ON 9212 80 .

ANNEX 1

Biochem. J. (1989) 253, 253-256 (Printed in Great Britain)

303

Isolation and sequence of a cDNA for human pro-(cathepsin L)

Susannah GAL* and Michael M. GOTTESMAN†

Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Building 37, Room 2E18, Bethesda, MD 20892, U.S.A.

The major excreted protein (MEP) of malignantly transformed mouse fibroblasts is the precursor to an acid proteinase with enzymic specificity similar to that of human cathepsin L. By cross-hybridization with a mouse MEP sequence, cDNA clones of the human form of MEP in an SV40 expression vector were isolated. A 1.6 kb cDNA showed 70% deduced amino acid sequence identity with mouse MEP. The deduced amino acid sequence of the cloned human MEP was the same, except for two amino acids, as the *N*-terminal sequence of mature human cathepsin L, thereby establishing that human MEP is human pro-(cathepsin L). Use of this human pro-(cathepsin L) cDNA clone allowed the detection of a 1.6–1.8 kb pro-(cathepsin L) mRNA in human cells which was not detected with a mouse pro-(cathepsin L) probe.

INTRODUCTION

Mouse fibroblasts which are malignantly transformed or stimulated by growth factors or tumour promoters synthesize and secrete increased amounts of a 39 kDa glycoprotein with acid-proteinase activity (Gottesman, 1978; Gottesman & Sobel, 1980; Doherty *et al.*, 1985; Rabin *et al.*, 1986; Frick *et al.*, 1985; Nilsson-Hamilton *et al.*, 1981; Gal & Gottesman, 1986a). This protein, termed 'MEP' (major excreted protein), is the precursor to two lower-*M*_r lysosomal proteins of 29 kDa and 21 kDa (Gal *et al.*, 1985), and contains the lysosomal recognition marker mannose 6-phosphate (Sahagian & Gottesman, 1982). Mouse MEP and human cathepsin L (Mason *et al.*, 1985) share amino acid bond cleavage specificities, catalytic constants and inhibitor susceptibilities (Gal & Gottesman, 1986b; Mason *et al.*, 1987). Comparison of the deduced amino acid sequences of mouse MEP, or a related protein called 'mouse cysteine proteinase', with a partial amino acid sequence for human cathepsin L, indicates strong similarity between these two sequences, but because of the species differences, does not prove identity (Troen *et al.*, 1987; Portnoy *et al.*, 1986; Denhardt *et al.*, 1986; Mason *et al.*, 1986).

In the present paper, we report the isolation and characterization of a full-length human MEP cDNA clone, isolated by cross-hybridization with a mouse MEP cDNA clone. The deduced amino acid sequence from this clone was identical, except for two amino acids, with that of the human cathepsin L sequence, proving that MEP is cathepsin L. This human cathepsin L cDNA can be used as a probe to determine the expression of cathepsin L mRNA in human cell lines and tissues.

MATERIALS AND METHODS

Isolation of a human cDNA clone for cathepsin L

The Okayama-Berg (1983) cDNA expression library termed 'GM637', made from mRNA isolated from SV40-virus-transformed human fibroblasts, was a gift

from Dr. Hirota Okayama (National Institute of Mental Health, National Institutes of Health, Bethesda, MD, U.S.A.). In all, 100 000 clones were screened on 20 filters by the technique of Troen (1987) for colony hybridization, using the 800-bp restriction-endonuclease-*Eco*RI fragment of mouse MEP (Troen *et al.*, 1987) labelled by nick translation (Loisstrand Laboratories, Gaithersburg, MD, U.S.A.). The filters were washed under moderate stringency conditions: twice with $2 \times \text{SSC}$ ($1 \times \text{SSC} = 0.15 \text{ M-NaCl}/0.015 \text{ M-sodium citrate}$)/1% SDS and twice with $0.8 \times \text{SSC}/1\%$ SDS at 60°C , and three positive clones were obtained. The clone designated 'pHu-16' contained the largest insert (1.6 kb) and was used for all subsequent studies.

Sequencing and blotting

Sequencing was done using the Sanger *et al.* (1977) dideoxy method with the Promega sequencing kit (Promega Biotech, Madison, WI, U.S.A.) and deoxyadenosine [α - ^{32}S]thiotriphosphate at a specific radioactivity of 500 Ci/mmol (NEN, Boston, MA, U.S.A.). pHu-16 was sequenced by using a combination of two techniques: (1) subcloning regions of pHu-16 DNA into Promega vectors pGEM-3 and pGEM-4 with Sp6 and T7 primers (Promega), and (2) direct sequencing using 50 ng of synthetic oligonucleotides (Applied Biosystems) as primers and the entire pHu-16 cDNA as template.

Detection of human procathepsin L RNA

RNA was isolated from tissue-culture cells as previously described (Chirgwin *et al.*, 1979; Maniatis *et al.*, 1982), and Northern blots were as described by Shen *et al.* (1986). Northern blots were probed with nick-translated *Eco*RI fragments from pHu-16 cDNA or pMMEP-14 cDNA (Troen *et al.*, 1987, 1988).

RESULTS AND DISCUSSION

Isolation and sequence of a human cathepsin L cDNA

We selected the human MEP clone by screening a cDNA library made from SV40-virus-transformed

Abbreviations used: MEP, major excreted protein.

* Present address: Friedrich-Miescher-Institut, P.O. Box 2543, CH-4002 Basel, Switzerland.

† To whom correspondence and reprint requests should be addressed.

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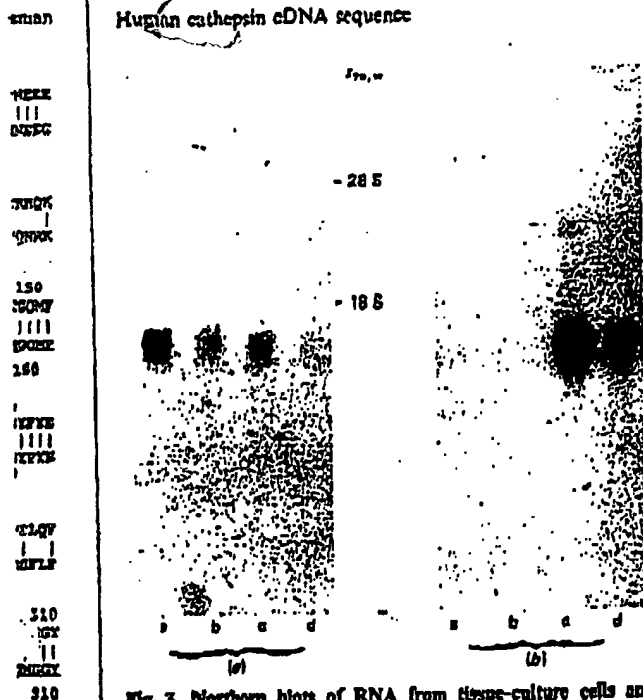


Fig. 3. Northern blots of RNA from tissue-culture cells and human tissues

(a) and (b), Northern blots of 10 μ g of total RNA from tissue-culture cells using two different probes. The sources of RNA were human KB cells (a), multidrug-resistant KB cells (b), mouse NIH 3T3 cells (c) and multidrug-resistant NIH 3T3 cells (d) as previously described (Shen *et al.*, 1986). In (a) hybridization was with the human pHu-16 *Eco*RI fragment and in (b) hybridization was with the *Eco*RI fragment from the mouse MEP clone pMMEP-14 (Troen *et al.*, 1987).

As for mouse MEP and mouse cysteine proteinase (Troen *et al.*, 1987; Portnoy *et al.*, 1986; Denhardt *et al.*, 1986), significant homologies were also observed when the human MEP sequence was compared with those of other cysteine proteinases, including cathepsin B, cathepsin H, actinidin and papain. Mouse and human forms of MEP show nearly identical sequences around amino acids Cys-138 and His-276 (Fig. 2), which are putative active sites on the basis of similarities to papain (Kamphuis *et al.*, 1985). Comparison of our sequence with those of several other human lysosomal proteins shows no obvious conserved signals for the lysosomal-protein-specific transfer of UDP-*N*-acetylglucosamine to the high-mannose chain to yield the lysosomal mannose 6-phosphate marker.

The *N*-terminal sequence of secreted mouse MEP indicates where pre-MEP is processed to yield MEP (Troen *et al.*, 1987). The deduced amino acid sequence of human prepro-(cathepsin L) also has the canonical Ala-Xaa-Ala sequence which precedes the leader-sequence cleavage site (Perlman & Halvorson, 1983) (Fig. 2). The positions of the *N*-terminal peptides of mature human cathepsin L within the deduced amino acid sequence of human MEP indicate the sites at which this precursor to human cathepsin L is processed to the lower *M*_r mature forms.

Because the full-length pro-(cathepsin L) cDNA which we isolated is cloned downstream from the SV40 promoter (Okayama & Berg, 1983), it is possible to express this cDNA in transfected cells. Recent experiments indicate that the human pro-(cathepsin L) cDNA is expressed in mouse NIH 3T3 cells as a 42 kDa protein that is secreted when it is overproduced (Kane *et al.*, 1988).

Use of the human procathepsin L cDNA to detect a procathepsin L mRNA in human cells

Fig. 3 shows the results of Northern blots with human KB (HeLa) cell and NIH 3T3 mouse-cell RNA probed with the *Eco*RI 800-bp fragment from the mouse and human MEP cDNA clones. The human probe recognized a 1.6-1.8-kb pro-(cathepsin L) message in human KB cells which migrated just below the 18S RNA marker (Fig. 3a) and appeared to be the same size as MEP mRNA from mouse cells (Fig. 3b). At high stringency, the mouse probe recognized a 1.6-1.8-kb RNA in mouse cells but no message in human cells (Fig. 3b). These data indicate that the human pro-(cathepsin L) cDNA described here (pHu-16) can be used to detect a human pro-(cathepsin L) mRNA, and that there is only one major pro-(cathepsin L) mRNA in cultured human KB cells. Preliminary results indicate that all normal human tissues tested express this pro-(cathepsin L) mRNA (results not shown). The availability of a full-length cDNA probe for human pro-(cathepsin L) will make it possible to assess relative levels of pro-(cathepsin L) mRNA in different tissues and in tumours.

We thank Dr. D.-w. Shen for RNA samples, Dr. H. Okayama for the human cDNA library, Dr. B. Troen, Mr. S. Smith and Dr. S. Kane for helpful discussions, Mr. S. Neal for photographic assistance, and Ms. J. Sharrar for secretarial help.

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S. Gal and M. M. Gottesman

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Received 10 February 1988/6 April 1988; accepted 25 April 1988

ANNEX 3(1)

00 01/05 WED 19:34

03 5531 5219 Sonoda & Kobayashi

OREAL

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Annex 8

SONODA & KOBAYASHI

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Cédric GALUP, Esq.
 Département de Propriété Industrielle
 L'OREAL
 6 rue Bertrand Siboholle
 92385 Clichy Cedex
 France

January 5, 2000

Your Ref: OA97128/JP/BN:CG
 Our Ref: JP1060LOR

Re: Japanese Patent Application No. Hoi 10-244055
 "Polypeptide isolated from the epidermis and its use"

Dear Mr. Galup:

Thank you for the front page of JP-A-H06-192124 (Toray). The following is an English translation of the paragraphs [0012] and [0013].

[0012]

Human cathepsin L is already known as one type of thiol protease (Mason et al., *Biochemical Journal*, **240**, 373-377, 1986), and its ability of elastin degradation (Mason et al., *Biochemical Journal*, **233**, 925-927, 1986) and an action of inactivating α 1-protease inhibitor (Johnson et al., *Journal of Biological Chemistry*, **261**, 14748-14751, 1986) have been reported.

[0013]

The prepro form of human cathepsin L consists of 333 amino acid residues (molecular weight of 38000), and the precursor (pro form) is the one in which N-terminal 1-17 residues are deleted. Namely, it comprises 18-333 residues (316 amino acid residues with molecular weight of 36000), and N-terminal amino acid sequence is as shown in Seq ID No: 1 of the sequencing list (Joseph et al., *J. Clin. Investigation*, **81**, 1621-1629, 1988). Among these, 18-113 residues are called activation peptide, 114-288 residues are a cathepsin H heavy chain, and 292-333 residues are a cathepsin L chain.

According to the paragraph [0015], the cathepsin L of the present invention includes precursor (18-333 residues), mature form (114-333 residues), H-chain (114-288 residues), L-chain (292-333 residues), and the precursor is preferable. Thus, the authors preferably use the procathepsin L. With respect to Mason et al., *Biochemical Journal*, **240**, 373-377, 1986 or Mason et al., *Biochemical Journal*, **233**, 925-927, 1986 or Johnson et al., *Journal of Biological Chemistry*, **261**, 14748-14751, 1986, it appears from the context of the above two paragraphs that they describe human cathepsin L or its prepro form or pro form or the like which are mentioned in the paragraph [0013]. Therefore, we presume that the human cathepsin L described in these documents are the same as those used by the authors.

We hope we have answered your question sufficiently, but should you have any questions, please do not hesitate to contact us.

Very truly yours,


 Yoshinori Kobayashi